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Thrombangitis obliterans: Leucocyte subpopulations and circulating immune complexes

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Summary

Background: The etiology of thrombangitis obliterans is still unclear. Although cellular infiltration of the vessel wall is known, no studies on peripheral blood mononuclear cells are reported. Therefore, we assessed leucocyte subpopulations and circulating immune complexes in patients with thrombangitis obliterans and a control group of normal people.

Patients and methods: 31 patients (40 ± 2 years, 24 male, 7 female) with thrombangitis obliterans were included, based on the following criteria: age of manifestation, acral ischemia in legs and arms, previous thrombophlebitis or phlebitis saltans. Manifestation of atherosclerosis or other vasculitic manifestations were excluded. Leucocyte subpopulations, levels of C-reactive protein (CRP) and circulating immune complexes (CIC) were investigated. An age-matched control group (n = 25) was recruited from voluntary blood donors.

Results: Leucocyte counts in the thrombangitis group (mean ± SD: 10 839 ± 782/nl) were significantly different from the control group (6205 ± 414/nl, p < 0.0001). The same was true for absolute counts of granulocytes, monocytes and lymphocytes. The results were independent from CRP, which was elevated only in 6 patients. Relative counts of naive helper T-cells were significantly lower in the patient group. HLA-DR expression on B-cells was lower on the patients' lymphocytes. The concentrations of IgA, IgG and IgM in CIC were higher in the thrombangitis patients compared to the control group. C1q-binding capacity and phosphatidylserine antibodies showed no differences.

Conclusions: Patients suffering from thrombangitis obliterans show alterations of leucocyte counts and their subpopulations as well as alterations of the humoral (IgCIC) immune system.

Key words

Thrombangitis obliterans, leucocyte subpopulation, circulating immune complexes, C-reactive protein

Zusammenfassung

Thrombangitis obliterans: Subpopulationen der Leukozyten und zirkulierende Immunkomplexe

Hintergrund: Die Ätiologie der Thrombangitis obliterans ist weiterhin ungeklärt. Obwohl histologisch eine zelluläre Infiltration der Gefäßwand vorliegt, wurden bisher keine Studien über periphere mononukleäre Zellen im Blut durchgeführt. Daher haben wir die Subpopulationen der Leukozyten und die zirkulierenden Immunkomplexe untersucht.

Patienten und Methoden: 31 Patienten (40 ± 2 Jahre, 24 Männer, 7 Frauen) mit Thrombangitis obliterans wurden eingeschlossen, nachdem die Diagnose an Hand folgender Kriterien gestellt wurde: Manifestationsalter, akrale Ischämie an Bein und/oder Arm, stattgehabte Thrombophlebitiden oder eine Phlebitis saltans und Ausschluss anderer entzündlicher Gefäßerkrankungen. Die Subpopulationen der Leukozyten, das C-reaktive Protein (CRP) und die zirkulierenden Immunkomplexe (CIC) wurden untersucht. Eine altersgemäße Kontrollgruppe (n = 25) wurde aus freiwilligen Blutspendern rekrutiert.

Ergebnisse: Die Anzahl der Leukozyten in der Thrombangitisgruppe (mean ± SD: 10 839 ± 782/nl) war signifikant höher als in der Kontrollgruppe (6205 ± 414/nl, p < 0.0001). Dasselbe galt für die Anzahl der Granulozyten, Monozyten und der Lymphozyten. Das Ergebnis war unabhängig vom CRP, welches nur bei 6 Patienten erhöht war. Die relative Anzahl der naiven Helfer T-Zellen war signifikant niedriger bei den Kontrollpatienten. Die HLA-DR Expression auf den B-Zellen war niedriger auf den Lymphozyten der Thrombangitispatienten. Die Konzentration von IgA, IgG und IgM in den CIC war höher bei den Thrombangitispatienten im Vergleich zur Kontrollgruppe. Die C1q-Bindungskapazität und die Phosphatidylserin-Antikörper zeigten keine Unterschiede.

Schlussfolgerung: Patienten, die an einer Thrombangitis obliterans leiden, zeigen sowohl Veränderungen der Anzahl der Leukozyten und ihrer Subpopulationen als auch des humoralen Immunsystems.

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Introduction

Thrombangitis obliterans is a rare disease, with clinical symptoms of peripheral arterial and venous occlusions. The prevalence in young men with peripheral arterial occlusive disease varies from 5% in young Caucasians to up to 16% in Asians [3, 19, 22]. Although this illness was first described almost 100 years ago, its underlying pathologic mechanisms are still unclear [4, 18, 20]. Histological investigations reveal cellular thrombus and cellular infiltration of the vascular wall, but with preservation of the wall structure [2, 22]. Gulati et al., using direct immune fluorescence microscopy in 10 patients, found various classes of immune globulins and C3 deposits in all layers of the involved vessels [8]. This result was confirmed by others and was further supported by elevated circulating immune complexes [13, 23]. Moreover, increased collagen type I and type III specific antibodies were found in patients with thrombangitis obliterans, compared with atherosclerotic or normal control subjects [1]. These results support the hypothesis of an immunologic aetiology for this disorder.

Although cellular infiltration of the vessel wall was described, no investigations of mononuclear cells were performed in peripheral blood until now. Therefore, we assessed counts of leucocytes and their subpopulations as well as circulating immune complexes in the patients with thrombangitis obliterans and the control group.

Patients and methods

In 1998 and 1999 a total of 31 patients with thrombangitis obliterans were studied. Because there were no clinical, radiological or laboratory findings proving thrombangitis obliterans, the diagnosis was based on established criteria summarised in Table I [1, 16, 18, 19]. All patients became symptomatic with acral ischemia of the feet, either with or without lesions. The mean age of the 24 male and 7 female patients was 40 ± 2 years. In 10 patients the onset of the symptoms was within the last six months before the investigation. 15 patients admitted ongoing intermittent nicotine abuse. An age-matched control group was recruited from 25 blood donors with a mean age of 39 ± 1 years. Data from the screening investigations excluded acute or previously relevant infections, manifest vascular diseases or diabetes mellitus. 11 blood donors currently smoked and 14 were non-smokers.

To confirm the diagnosis of patent proximal arteries and occluded crural or foot arteries, and to exclude atherosclerotic intima lesions, color Doppler sonography was performed in all patients and angiography in 25 patients. Echocardiography was carried out to exclude cardiac origin of emboli. Medical history was evaluated regarding nicotine abuse, Diabetes mellitus or traumatic events. Digital artery Color duplex sonography was performed to confirm or exclude arterial occlusions of the upper limb arteries [15]. Patients, and the referring physicians, were asked for previous thrombotic or phlebitic disorders. To exclude patients with arterial manifestation of connective tissue disease such as scleroderma, lupus erythematodes or others, only those with negative antinuclear antibodies (ANA), extractable nuclear antibodies such as Jo1, RNP, SSA, SSB, SM, SCL70 and double stranded-DNA antibodies were accepted as thrombangitis patients.

Table I: Clinical profile of the patients supposed to have thrombangitis obliterans.

Criteria	Number	%
Age of manifestation < 40	31	100
Nicotine abuse	31	100
Distal arterial occlusions: leg	31	100
Acral lesion	21	68
Distal arterial occlusions: arm	12	39
Prior thrombosis, phlebitis	14	45
No diabetes mellitus	31	100
No hypertension	31	100
Negative ANA, ENA, ds-DNA etc.	31	100
Typical histological findings	4	17

From each patient and control individual venous blood samples were taken in the morning. The following parameters were investigated:

C-reactive protein (CRP)

Serum CRP concentrations were estimated with the Array 360 nephelometer (Beckman Coulter, München, Germany)

Cell counting and flow cytometry

From EDTA blood samples the leucocytes were counted using an electronic cell counter (Sysmex®, Hamburg, Germany). Whole blood leucocytes were differentiated into three groups by flow cytometry, using monoclonal antibodies (MoAb), fluorescein isothiocyanate (FITC)-conjugated anti-CD45 (all leucocytes), and phycoerythin (PE)-conjugated anti-CD14 (monocytes).

To detect lymphocyte subpopulations, the following MoAb were used: FITC-coupled anti-CD3 (T cells) and PE-conjugated anti-CD19 (B cells); FITC-coupled anti-HLA-DR (activated T lymphocytes, clone L234) and PE-conjugated anti-CD3; FITC-coupled anti-HLA-DR and PE-conjugated anti-CD19. NK cells were defined as CD16+(FITC), CD56+(PE), CD3-(PerCP) and, therefore, analysed by three-color flow cytometry. Helper (FITC-coupled anti-CD4) and cytotoxic (PE-coupled anti-CD8) T cells (PerCP-conjugated anti-CD3) were examined by three-color flow cytometry as activated CD25+ (PE-coupled anti-CD25, interleukin 2 receptor) T-helper and T-cytotoxic lymhocytes. Three color flow cytometry was also used to identify naive (PE-coupled anti-CD45RA) or memory (PE-coupled anti-CD45RO) T-helper cells. All MoAb were obtained from Becton Dickinson, Heidelberg, Germany. The density of HLA-DR molecules/cell was measured as mean fluorescence intensity (MFI) in arbitrary channels of energy as previously described [6]. To calculate MFI we used a linear format to express mean channel fluorescence intensities as numerals.

In short, 200 µl phosphate buffered saline (PBS) were added to 20 µl of the above mentioned MoAb combina-

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tions. After addition of 100 µl EDTA-blood, samples were incubated in darkness for 15 minutes. The erythrocytes were lysed with lysing solution (Becton Dickinson) and then washed with PBS. Stained cells were measured with a FACS Calibur (Becton Dickinson).

Circulating immune complexes (CIC)

700 µl serum were centrifugated (15 000×g, 15 min, 4°C) and 500 µl of the supernatant mixed with 125 µl 9.6% polyethylene glycol (PEG, Merck, Darmstadt, Germany)/ 0.07 m EDTA/veronal buffer-solution and incubated for 24 hours (4°C, ice bath). After centrifugation (5 000×g, 20 min 4°C) the pellet was washed with 1.7% PEG, centrifugated (4 000×g, 15 min, 4°C), and resuspended in 500 ml veronal buffer. After over-head mixing for 1 hour the sample was incubated (30 min, 37°C). IgA, IgG and IgM concentrations were measured with the Array 360 nephelometer (Beckman Coulter).

CIC-C1q concentrations

The CIC-C1q measurement in serum is based on the principle that complement CIC fixing will bind to immobilised human C1q purified protein, and this was performed using the CIC-C1q test of Quidel (San Diego, CA, USA).

Anti-phosphatidylserine antibody (APSA) concentrations

APSA concentrations of the IgG or IgM class were examined with an enzyme-immunoassay of Imtec (Berlin, Germany).

Out of the 25 control subjects, no EDTA blood was received from 3 of them. Out of the 31 patients, no serum was available from 1. The other missing values were due to technical or procedural failures.

Statistics

The two-tailed Wilcoxon test was performed for comparison of cell and immunoglobulin concentrations between patients and the control group. Frequencies of elevated CRP levels were compared between patients and control group, using the chi-square test. The level of significance was designated at $p < 0.05$. Statistics were performed using statistical analysis software (SAS Institute, Cary, NC, USA).

Results

Cell counts

The leucocyte counts of the thrombangitis patients slightly exceeding the upper normal limit of 10 000 cells/nl were significantly higher than the values of the blood donors (Table II). Absolute counts of granulocytes, monocytes and lymphocytes, as well as lymphocyte subpopulations, were also significantly higher in the patients. In contrast, relative counts of naive helper T-cells were significantly lower in the patient group.

The sum of relative counts of both naive and memory helper T-cells of the control group was higher at 58% than the relative count of helper T-cells (45%). This is explainable through 13% $CD45RA^+CD45RO^+$ T-helper cells; all these carry naive and memory cell characteristics. In contrast, the sum of the relative counts of naive and memory helper T-cells of the patients (48%) was about the same as the helper T-cell count (46%). HLA-DR expression (MFI values) of B-cells was significantly lower on the 25 patients tested, compared with the MFI values of the B cells of the control group.

Only six patients had elevated CRP levels (> 0.5 mg/dl), whereas all blood donors had normal CRP concentrations ($p < 0.05$). After exclusion of these 6 patients from analysis, the results described previously remained significantly different.

To exclude the influence of smoking we did a separate analysis of the non-smoking sub-groups of the thrombangitis patients and the control group (Table III). The re-analysis corroborate the relevant results regarding the T-cells.

Circulating immune complexes

The concentrations of IgA, IgG and IgM in circulating immune complexes were significantly higher in the thrombangitis patients than in the control group (Table IV). The C1q-binding of immune complexes was significantly lower. The concentrations of IgA, IgG and IgM remained significantly different, when reproduced in the non-smoking sub-groups (Table III).

Determination of antiphosphatidylserine antibodies revealed no significant differences between patients and control group.

The comparison of the 10 patients with onset of the symptoms within the last six month and those with a longer course of the disease revealed no relevant differences for all analysed parameters.

Discussion

The diagnosis of thrombangitis obliterans is made by exclusion of other vascular disorders such as atherosclerosis, peripheral embolism or connective tissue disease, and by confirmation of the characteristic criteria given in Table I. The number of females is rather high at 25%, but this has been reported before, and an increasing number of female patients with thrombangitis obliterans was found in the last decades [5, 9, 15, 17, 20]. A mean age of 40 years in our patients is similar to that of other study groups [1, 13, 16, 26].

The most prominent observation of this study was the leucocyte counts at the upper borderline in the thrombangitis patients which has, as far as we know, not been published yet. However, such leucocyte counts in themselves are not diagnostic. To confirm that these results were as-

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Table II: Peripheral blood mononuclear cell counts and mean fluorescence intensity (MFI) values in thrombangitis patients and blood donors (SEM: standard error of mean, MFI: mean fluorescence intensity, NS: not significant).

		Thrombangitis obliterans			Blood Donors			
		N	Mean	SEM	n	Mean	SEM	p-value
Leucocytes	Cells/nl	31	10839	782	22	6205	414	0.0001
Granulocytes	Cells/nl	31	7383	751	22	3923	317	0.0001
Granulocytes	%	31	65	2	22	62	1.7	NS
Monocytes	Cells/nl	31	631	66	22	431	32	0.0051
Monocytes	%	31	6	0,5	22	7.1	0.4	NS
Lymphocytes	Cells/nl	31	2815	211	22	1851	135	0.0017
Lymphocytes	%	31	29	2	22	31	2	NS
B-cells	Cells/nl	31	462	56	22	205	15	0.0011
B-cells	%	31	15.6	1.4	22	11.5	0.9	0.0538
HLA-DR on B-cells (MFI)	Channels	25	171	2	22	181	2	0.0055
T-cells	Cells/nl	31	2035	167	22	1367	118	0.0041
T-cells	%	31	72	1	22	73	1.3	NS
Helper T-cells	Cells/nl	31	1332	131	22	839	66	0.0031
Helper T-cells	%	31	46	1	22	45	1.7	NS
Memory helper T-cells	Cells/nl	30	879	96	22	606	53	0.0485
Memory helper T-cells	%	30	30	2	22	33	2.1	NS
Naive helper T-cells	Cells/nl	30	536	69	22	459	47	NS
Naive helper T-cells	%	30	18	2	22	25	1.9	0.0081
Cytotoxic T-cells	Cells/nl	31	630	63	22	461	64	0.0168
Cytotoxic T-cells	%	31	23	2	22	24	1.7	NS
HLA DR on T-cells (MFI)	Channels	29	164	1	22	162	2	NS
HLA DR+ T-cells	Cells/nl	31	35	6	22	22	3.8	NS
HLA DR+ T-cells	%	31	1.2	0.1	22	1.1	0.1	NS
CD 25+ T-cells	Cells/nl	31	355	42	22	246	25	NS
CD 25+ T-cells	%	31	12	1	22	13	0.9	NS
NK-cells	Cells/nl	30	100	18	22	63	11	NS
NK-cells	%	30	4.2	0.8	22	3.4	0.7	NS

sociated with the disease thrombangitis, other inflammatory processes had to be ruled out. Therefore, an exact medical history was obtained, and measurements of antibodies specific for vasculitic and collagenous diseases were checked. In addition, the patients had no elevated antiphosphatidylserine antibodies. These antibodies were most common in women with recurrent spontaneous abortions, which would occur due to a vascular insufficiency of the placenta [16]. Although six patients had elevated CRP levels, significantly elevated leucocyte counts were found to be independent from CRP-levels. In the patients with normal CRP-levels, chronic bronchial infections or an acute phase reaction due to local ischemia, could be excluded. Moreover, elevated CRP levels were mainly due to local infections and not to a systemic inflammation. Thus, increased leucocyte counts can be assumed to be associated with thrombangitis obliterans itself. At the moment we have no explanation for this phenomenon.

There is also only little data on CRP levels in thrombangitis patients. One study, including 31 patients, reported elevated CRP levels in 15 patients [19]. This study gave no additional information as to whether the elevation was due to secondary problems, e.g. bronchitis, sinusitis or an infected gangrene. In our study, 5 of the 6 patients with elevated CRP levels had local infections as a potential cause of raised CRP concentrations. In the remaining 25 patients, normal CRP concentrations excluded significant infections.

An increased number of total blood leucocytes was reported in smokers, compared to non-smokers, independent from the underlying disease [11]. With 7400–7900 leucocytes/nl (95% CI) versus 5600–6000 the differences were not as great as the ones we found. Information about an association with CRP levels was not given in this study. In contrast, in our findings the elevation of total blood leucocytes in the thrombangitis patients was shown to be mainly due to increased total blood neutrophils, and not lymphocytes. Cigarette smokers were also reported as having a significantly lower proportion of natural killer cells than probands who had never smoked [24], and a selective increase in CD4+ helper T cells compared with non-smokers [25]. Differences in smoking behaviour between the

Table III: Results of the reanalysis of the non-smokers in the thrombangitis patients and the blood donors.

Non-smokers only		Thrombangitis obliterans			Blood donors			p-value
		n	mean	SEM	n	mean	SEM	
Leucocytes	Cells/nl	16	10944	1348	14	6000	468	0.0005
Naive helper T-cells	%	16	18	3	14	27	2	0.0093
HLA-DR on B-cells (MFI)	Channels	16	172	3	14	183	2	0.0087
CIC-IgA	mg/dl	16	4.1	0.4	14	2.7	0.2	0.0010
CIC-IgG	mg/dl	16	17.8	2.5	14	10.6	0.9	0.0073
CIC-IgM	mg/dl	16	12.9	1.6	14	7.8	0.8	0.0246

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Table IV: Concentrations of circulating immune complexes (CIC) and antiphosphatidylserine antibodies (APSA) in thrombangitis patients and blood donors. (SEM: standard error of mean, NS: not significant).

		Thrombangitis obliterans			Blood donors			p-value
		n	mean	SEM	n	mean	SEM	
CIC-C1q	µg Eq/ml	30	1.6	1.3	25	3.3	1.5	0.0028
CIC-IgA	mg/dl	30	3.9	0.3	25	2.8	0.1	0.0002
CIC-IgG	mg/dl	30	17.8	1.8	25	11	1	0.0017
CIC-IgM	mg/dl	30	14.6	2.6	25	8	1	0.0018
APSA IgG	U/ml	30	6.2	1.1	25	4.0	0.6	NS
APSA IgM	U/ml	30	8.7	1	25	8.1	1	NS

thrombangitis patients and the control group cannot explain our findings. Excluding the smokers and re-analysing the non-smokers only confirmed the differences in leucocytes and naive helper T-cells. Thus these findings can be assumed to be due to the underlying thrombangitis.

We found the fraction of naive helper T-cells significantly decreased, which may be due to a decreased number of $CD45RA^+/CD45RO^+$ double positive helper T-cells. This conclusion is based on the comparison of the sum of naive and memory helper T-cells (48%] with the helper T-cell count (46%). Hamann et al. described that the sum of the separately counted naive and helper T-cells together out-numbers the total helper T-cell count by 18% normally, because of a fix number of helper T-cells carrying both markers [10]. In our analysis, the calculation revealed a sum of 58% naive and memory helper T-cells, compared to 45% helper T-cells in the control group. Therefore, 13% T-helper cells carry CD45RA and CD45RO. These double positive cells are able to provide help for B-cells [10]. The deficit of this double positive helper T-cell subset in the patients may be associated with limited function of the B-cells, as the significantly decreased HLA-DR expression suggests. Although the counts are increased, the B-cells of the patients express significantly fewer HLA-DR molecules than those of the healthy blood donors. The reduced density of HLA-DR molecules may be associated with a disturbed function, because HLA-DR molecules are required for antigen presentation and are expressed on the surface of adept antigen-presenting cells such as macrophages, dentritic cells and B-cells [6].

Previous studies on circulating immune complexes reported elevated levels of immunoglobulines (IgG, IgA, IgM) and increased deposition along the internal elastic lamina [8,12,13, 17, 23]. We found increased concentrations of IgA, IgM and IgG immunoglobulins in the circulating immune complexes. But the increased concentrations were not associated with an increased C1q binding. The data of Lamprecht et al. corroborate our observations [13]. The presence of circulating immune complex concentrations without C1q binding capacity may have pathogenetic relevance, as normally circulating immune complexes lead to tissue destruction at the site of deposition by complement activation. However, tissue destruction is not the predominant feature of thrombangitis obliterans. Therefore, the pathomechanism leading to thrombangitis obliterans seems to be explained by the deposition of circulating immune complexes along the internal elastic lamina, the subsequent binding of mononuclear cells to the endothel and finally thrombotic occlusions [12]. Severe complement mediated tissue damage, typical for vasculitis or glomerulonephritis, does not occur.

Conclusion

This study reveals some evidence for an immunologic imbalance in thrombangitis patients independent from smoking. Further investigations with long-term follow-up are necessary to discriminate changes due to acute stages and remission.

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